AWARD NUMBER: W81XWH-11-1-0626

TITLE: Treatment of Fragile X Syndrome with a Neuroactive Steroid

PRINCIPAL INVESTIGATOR: Randi Hagerman, M.D.

CONTRACTING ORGANIZATION: University of California, Davis
Sacramento, CA 95817

REPORT DATE: August 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2015	Annual	15 Jul 2014 – 14 Jul 2015

4. TITLE AND SUBTITLE
Treatment of Fragile X Syndrome with a Neuroactive Steroid

5a. CONTRACT NUMBER
W81XWH-11-1-0626

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Randi Hagerman, M.D.

E-Mail: rjhagerman@ucdavis.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, Davis
MIND Institute
2825 50th Street
Sacramento, CA 95817

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a Phase II trial to assess the safety, tolerability, and efficacy of ganaxolone, a GABAA agonist, for the treatment of behavioral problems, including anxiety and inattention in children with FXS. It has been demonstrated in the fragile X mouse model and the Drosophila (fruit fly) models of FXS that the GABAA system, including multiple receptors, is dramatically down-regulated. Ganaxolone is a drug that enhances GABAA activity. We hypothesized that ganaxolone will significantly improve behavioral problems such as anxiety, inattention, and impulsivity problems in children with fragile X syndrome. We planned to enroll 60 children, ages 6-17 years, with fragile X syndrome over a 4-year period and they would be randomized to receive either ganaxolone or a placebo initially and then crossed over after 6 weeks. We have used innovative outcome measures in addition to standard outcome measures that have been successful in previous treatment trials in fragile X syndrome at baseline and follow-up visits.

15. SUBJECT TERMS

Nothing Listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	UU	6	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

1. INTRODUCTION

This study is a Phase II trial to assess the safety, tolerability, and efficacy of ganaxolone, a GABAA agonist, for the treatment of behavioral problems, including anxiety and inattention in children with FXS. It has been demonstrated in the fragile X mouse model and the *Drosophila* (fruit fly) models of FXS that the GABAA system, including multiple receptors, is dramatically down-regulated. Ganaxolone is a drug that enhances GABAA activity. We hypothesized that ganaxolone will significantly improve behavioral problems such as anxiety, inattention, and impulsivity problems in children with fragile X syndrome. We planned to enroll 60 children, ages 6–17 years, with fragile X syndrome over a 4-year period and they would be randomized to receive either ganaxolone or a placebo initially and then crossed over after 6 weeks. We have used innovative outcome measures in addition to standard outcome measures that have been successful in previous treatment trials in fragile X syndrome at baseline and follow-up visits.

2. KEYWORDS:

fragile X syndrome, targeted treatments, ganaxolone, GABAA agonist, controlled treatment trial.

3. OVERALL PROJECT SUMMARY

TASKS 1, 2 and 3 were completed in the beginning of Year 2. Regarding TASK 4, we are actively recruiting subjects at a rate of 3–4 individuals per month to meet the enrollment goal of sixty. From Jul 15, 2014 to Jul 14, 2015, 14 subjects were enrolled, screened, and randomized, bringing the total enrollment to 50. Thirty-five have completed; there have been eight early terminations and two screen failures. We currently have 5 patients in the active protocol and they will finish in the fall of 2015. No serious adverse events have occurred. Data-entry is being completed on a regular basis. At the end of the last patient completion, we will start the statistical analysis with Dr. Danh Nguyen. We have been in active communication with him and have put through a mock data set; he is ready to analyze the data once we have finalized all of the data. The second Data Safety Monitoring Board (DSMB) meeting took place in January 2015, and the trial was allowed to proceed.

Work on TASK 5, data-analysis and report writing, is in the preliminary stages. We are currently preparing for data-analysis using test data in anticipation of study close. We plan on having data-analysis and report writing completed by the end of Year 5.

4. KEY RESEARCH ACCOMPLISHMENTS

* We have studied 50 patients with fragile X syndrome in a controlled trial, and they have tolerated ganaxolone well without significant adverse effects.
* Ganaxolone is safe in children with FXS between the ages of 6 to 17yo.
* We do not yet know the efficacy of ganaxolone in FXS, but we hope to have this data by early 2016 once our analysis is complete.

5. CONCLUSION

Ganaxolone is a targeted treatment in fragile X syndrome that is safe in children 6 to 17yo. Our research will demonstrate whether this treatment is efficacious in children with FXS for treatment of anxiety or other behavioral problems. We will soon have our efficacy data. If this medication is efficacious, we will work with Marinus Pharmaceuticals, who makes ganaxolone, to get it FDA approved. If it does not demonstrate efficacy, we may consider further trials where ganaxolone is combined with other targeted treatments.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. ***List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts.***

1. Lay Press:

Lozano R, Hare EB and Hagerman RJ (2014) Fragile X-associated disorders. In: Rosenberg RN, Pascual JM (eds) Rosenberg's Molecular and Genetic Basis of Neurologic and Psychiatric Disease: Fifth Edition. Academic Press, London, UK, pp 183-195 ISBN: 9780124105294 https://books.google.com/books?id=HT3LAwAAQBAJ&lpg=PA183&ots=0CvsBgBixj&dq=Rosenberg%E2%80%99s%20Molecular%20and%20Genetic%20Basis%20lozano&pg=PA183#v=onepage&q=Rosenberg%E2%80%99s%20Molecular%20and%20Genetic%20Basis%20lozano&f=false

2. Peer-Reviewed Scientific Journals:

Yang JC, Niu YQ, Simon C, Seritan AL, Chen L, Schneider A, Moghaddam ST, Hagerman PJ, Hagerman RJ and Olichney JM (2014) Memantine Effects on Verbal Memory in Fragile X-associated Tremor/Ataxia Syndrome (FXTAS): a Double-Blind Brain Potential Study. *Neuropsychopharmacology* 39:2760-2768. PMID24871547, http://www.ncbi.nlm.nih.gov/pubmed/24871547

Lozano R, Rosero CA and Hagerman RJ (2014) Fragile X spectrum disorders. *Intractable Rare Dis Res* 3:134-146. PMID25606363, PMC4298643 http://www.irdrjournal.com/getabstract.php?pmid=25606363

3. Invited Articles: N/A

4. Abstracts: N/A

b. ***List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.***

New treatments for fragile X syndrome and autism, Seminar, Hautepierre Hospital, Strasbourg, France, 3/9/2015

Targeted Treatments for Fragile X Syndrome, Keystone Symposia, Granlibakken Resort, Tahoe City, 3/17/2015.

Targeted treatments for fragile X syndrome, Fragile X Conference, Karolinska University Hospital, Stockholm, Sweden, 5/7/2015.

New treatments for fragile X and autism, Conference on Rare Diseases, Frambu Centre for Rare Disorders, Siggerud, Norway, 5/29/2015.

7. INVENTIONS, PATENTS AND LICENSES: N/A

8. REPORTABLE OUTCOMES

We have discussed ganaxolone as a targeted treatment for FXS in many papers and reviews. Ganaxolone represents a group of GABAA agonists that are likely to be efficacious in FXS, and we have shown that it is safe in children 6 to 17 yo.

9. OTHER ACHIEVEMENTS

We are also assessing the biomarkers that may improve with ganaxolone; this will be part of the trial results that will be analyzed in the fall of 2015 once all of the data is obtained.

10. REFERENCES

N/A

11. APPENDICES

N/A